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Multiple Bilobar Liver Metastases: Cryotherapy for Residual Lesions After Liver Resection

PETER M. HEWITT, FCS (SA), SIMON J. DWERRYHOUSE, FRCS (Eng), JING ZHAO, M MED SCI, AND DAVID L. MORRIS, PhD*

Department of Surgery, University of New South Wales, St. George Hospital, Kogarah, Sydney, Australia

Background and Objectives: Most patients with colorectal liver metastases are not eligible for resection because they have multiple lesions or because of anatomical constraints. We report the use of cryotherapy to destroy residual metastases following liver resection in patients with disease too widespread for treatment by resection alone.

Methods: Twenty patients with bilobar disease confined to the liver (median 3; range 2–8 lesions) were treated in this way. Seventeen patients also received regional chemotherapy postoperatively.

Results: Morbidity was high, but there were no procedure-related deaths and only one patient's hospital stay exceeded 24 days. Significant destruction of tumor, as evidenced by a decline in CEA levels, occurred within 3 months of surgery in all patients ($P < 0.001$). Median duration of follow-up was 15 (6–53) months. Survival rates at 1 and 2 years were 88% and 60%, respectively, and median survival was 32 months. Seven patients remain well and seven are alive with recurrent liver and/or other metastases.

Conclusions: Although this is not a control study, it would appear that some patients with irresectable liver metastases benefit from this multimodality approach. *J. Surg. Oncol. 1998;67:112–116.*

KEY WORDS: bilobar liver metastases; synchronous resection and cryotherapy

INTRODUCTION

Resection of colorectal metastases confined to the liver is the optimal management option [1,2] and is thought to be the only modality that can offer a potential cure, with 5-year survival rates of up to 40% or greater in good prognostic groups [3–7]. However, this treatment is not applicable in the majority of patients who develop liver metastases, even those with no extrahepatic disease, because they have four or more lesions, or because of anatomical constraints [4,5].

Hepatic cryotherapy is a method that has been used to achieve imaging-controlled destruction of metastases in patients with limited, but irresectable disease, with promising results [8–10]. There are also two situations where cryotherapy may be useful as an adjunct to liver resection: edge cryotherapy for inadequate or involved resection margins (edge), or cryoablation of residual lesions in the remaining liver after a formal resection (contralobe). Neither has been described in detail or results reported. This report details our experience in 20 patients undergoing cryotherapy to residual liver metastases (contralobe) following liver resection.

MATERIALS AND METHODS

During the period February 1992 to April 1997, 20 patients with bilobar liver metastases from colorectal cancer underwent synchronous liver resection and cryotherapy. In all these cases, the disease was deemed irresectable by surgery alone (D.L.M.). Median age of the

*Correspondence to: Professor David L. Morris, Clinical Sciences Building, St. George Hospital, Kogarah, Sydney 2217, Australia. Fax No.: (61)2-9350-3997.

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TABLE I. History of the 20 Patients With Multiple Liver Metastases

Patient no.	Sex	Age	Primary site	Primary surgery[a]	Dukes stage[b]	Interval to liver surg. (mo)	Date of liver surg.
1	M	71	sigmoid	SC	S	4	7/2/92
2	M	78	sigmoid	SC	S	1	27/3/92
3	F	59	rectum	AR	C	39	2/2/93
4	M	69	sigmoid	SC	B	40	19/2/93
5	F	53	rectum	AR	C	18	21/1/94
6	M	71	rectum	APR	C	17	17/5/94
7	M	69	rectum	AR	B	19	10/6/94
8	M	72	ascending	RHC	B	24	15/11/94
9	M	59	caecum	RHC	C	6	24/1/95
10	F	55	rectum	AR	S	9	16/5/95
11	F	54	sigmoid	SC	S	2	19/5/95
12	M	66	rectum	APR	S	0	24/5/95
13	F	71	descending	LHC	S	2	4/7/95
14	M	43	rectum	AR	C	8	15/8/95
15	F	64	ascending	RHC	C	11	10/10/95
16	F	52	ascending	RHC	S	45[c]	21/11/95
17	F	72	transverse	TVC	S	3	5/12/95
18	M	67	ascending	RHC	B	12	29/3/96
19	M	58	rectum	AR	C	3	15/10/96
20	M	63	sigmoid	SC	B	12	18/4/97

[a]SC = sigmoid colectomy; AR = anterior resection; APR = abdominoperineal resection; RHC = right hemicolectomy; LHC = left hemicolectomy; TVC = transverse colectomy.
[b]S = synchronous liver metastases.
[c]Patient had previous cryotherapy and regional chemotherapy 3 months after RHC; i.e., this was the second attempt at ablation of liver metastases.

patients was 65 (43–78) years, and 12 of them were men (Table I). All patients were considered fit for major abdominal surgery, and none had evidence of extrahepatic disease on preoperative screening consisting of clinical assessment, chest X-ray, CT scan of chest and abdomen, CT portography, and bone scan. Eight patients had liver metastases at the time of bowel surgery, and 12 developed metachronous lesions. The interval from initial bowel surgery to liver surgery varied from 0–45 (median 9) months; in one patient the liver surgery was a combined procedure together with bowel resection, whereas another had synchronous cryotherapy and liver resection 42 months after previous cryo- and regional chemotherapy.

Initially, patients underwent laparotomy via a right subcostal incision to ensure that there was no extrahepatic disease and any suspicious lymph nodes, peritoneum, etc., were submitted for frozen section histology. At the same time, intraoperative ultrasound was used to assess the extent of liver disease. The incision was then extended (tri-radiate) and the liver was fully mobilized. The dominant metastases were resected using portal inflow occlusion and an ultrasonic dissector to minimize blood loss. Remaining liver lesions were treated by cryoablation (two freeze-thaw cycles to each lesion). This was delivered via spike probes using the Cryotech™ LCS 3000 liquid nitrogen system (Spembly, Andover, UK) as previously described [11]. A hepatic artery catheter was also placed for infusion of chemotherapy in 16 patients; three were unsuitable, (two because of technical difficulties and one because of intraoperative decompensation). A portal vein catheter was placed in the patient who had concurrent bowel resection because of an arterial anomaly.

After discharge from the hospital, patients were monitored by 3-monthly clinical review and CEA levels. Abdominal CT scans were performed yearly, or at other intervals where appropriate based on clinical or laboratory criteria. Survival times were calculated from the date of liver surgery and a survival curve was constructed using the Kaplan-Meier method. Other quantitative data was analyzed using Student *t*-test (Statistica version 5 for Windows™ computer package).

RESULTS

The median number of liver lesions were three (2–8) per patient (Table II). In all instances where there were less than four lesions, the disease was bilobar. A total of 33 lesions were treated by resection (median 1/patient; range 1–5) and 40 were managed by cryotherapy (median 2/patient; range 1–6). The types of liver resection included 10 left lateral segmentectomies (3 with part of segment 4), 2 right lobectomies, 1 central resection, 3 involving two right hepatic segments, and 4 monosegmental resections. The median operating time (including anesthetic time) and hospital stay were 270 (180–

TABLE II. Liver Surgery and Cryotherapy in the 20 Patients With Multiple Liver Metastasis

Patient no.	Extent of resection(s) (segments)	**Diameter(s) resected lesion(s) (mm)**	Extent of cryotherapy (segments)	**Diameter(s) cryotherapy lesion(s) (mm)**	HAC[a]	Blood loss (ml)
1	5, 6, 7, 8	**120 (+satellites)**	2	**10**	Yes	2,090
2	2, 3	**40**	4, 8	**30, 5**	Yes	-
3	5, 6	**70**	4	**20**	Yes	-
4	6, 7	**100**	4	**30**	No[b]	2,800
5	2, 3 (part 4)	**120**	1, 4, 8	**6 × 10–20**	Yes	1,270
6	2, 3	**30, 20**	6	**20**	Yes	800
7	2, 3	**5 × 7–35**	4, 8	**3 × <10**	Yes	2,000
8	6, 7	**35, 15**	4	**3**	Yes	800
9	2, 3	**30**	5, 6	**20, 15**	No[c]	-
10	2, 3 (part 4)	**130, 55**	5, 6, 7, 8	**30, 3 × 10**	Yes	950
11	2, 3	**80**	7	**20, 10**	Yes	300
12	2, 3	**30**	8	**<10**	PV[d]	900
13	2, 3	**80**	7	**50**	Yes	750
14	4a	**35**	6	**20**	Yes	-
15	4a (part 2,3,6)	**40, 35, 15, 1**	3	**5**	Yes	450
16	3	**20, 0.5**	4	**30, 10**	No[c]	500
17	2, 3 (part 4)	**20**	6	**10**	Yes	550
18	5, 6, 7, 8	**30, 20, 10**	2	**5**	Yes	500
19	4b	**30**	1, 4, 5, 6	**40, 30, 15, 10**	Yes	-
20	6	**40**	3, 4, 6	**25, 15, 10**	Yes	-

[a]Hepatic artery catheter.
[b]Intraoperative decompensation.
[c]Technical problems.
[d]Portal vein catheter because of arterial anomaly.

455) minutes and 11 (range 6–61) days respectively. The median intraoperative blood loss was 850 (300–2,800) ml. Postoperative complications occurred in eight patients, but there were no 30-day or procedure-related deaths (Table III). The patient who stayed in hospital for 61 days developed a bile leak, which was complicated by septicemia and pulmonary embolism. However, he made a complete recovery after prolonged intensive care management and survived for 46 months.

Intra-arterial chemotherapy (5FU 1 g/day in combination with oral folinic acid—15 mg tds), given for 4 days at 2 weekly intervals, was not associated with any systemic toxicity, and CEA levels declined dramatically in 18 of the 20 patients within 3 months of surgery ($P < 0.001$) (Table III). (Because CEA data was skewed, logarithmic values were analysed.) In one patient, therapy had to be discontinued because of major hemorrhage related to a hepatic artery aneurism, whereas development of metastases elsewhere necessitated conversion to systemic chemotherapy in another eight patients.

Median duration of follow-up was 15 (6–53) months. Survival rates at 1 and 2 years were 88% and 60%, respectively. Median survival was 32 months. Seven patients remain well and free of disease and seven are alive with recurrent liver and/or other metastases. Six patients have died; five with recurrent cancer and one from an unrelated cause. A survival curve for the whole group of patients is shown in Figure 1.

DISCUSSION

The use of cryotherapy to extend the role of liver resection has not previously been reported in any detail. This study describes the use of both modalities in patients who would otherwise have received chemotherapy alone, with very little prospect of long-term survival.

Postoperative morbidity in this series was considerable, but there were no procedure-related deaths and only one patient's stay exceeded 24 days. Three patients required re-operation: one for reactionary hemorrhage; two for small bowel obstruction. Bile leakage accounted for most morbidity and was probably a function of resection. In all cases, bilomas were drained radiologically, obviating the need for a second operation. Although bile ducts are susceptible to cryo-injury [12], we have not experienced this complication after cryotherapy alone. Regional chemotherapy was also associated with some morbidity. One patient had a major intraperitoneal bleed several months after liver surgery, which was due to a false aneurism of the hepatic artery. In another patient, fatal upper gastrointestinal bleeding may have been related to chemotherapy, but we were unable to verify this as he was treated at another center. Vascular complications associated with intra-arterial chemotherapy have been reported by our group previously [13].

Our data suggest that significant destruction of tumor occurred initially in the majority of patients, as evidenced

TABLE III. Results of Cryotherapy for Residual Lesions After Liver Resection

Patient no.	Morbidity (hosp days)[a]	CEA-pre (ng/ml)	CEA-3 mo (ng/ml)	Alive/dead	Liver recurrence (Y/N) (other metastasis)[d]	Follow-up (months)
1	biloma (19)	4,110.0	128.0	D	Y (bone)	11
2	N (9)	68.0	3.7	A	N	53
3	biloma (11)	14.4	1.6	D	Y (lung)	24
4	bile leak; PE (61)	36.0	2.0	D	Y (bone; scar}	46
5	hematoma (6)	92.0	10.0	D	Y (lung; LNs)	15
6	N (10)	19.5	1.5	D[b]	N	6
7	hemorrhage (11)	46.3	4.0	A	N	35
8	liver abscess (14)	19.2	3.5	A	Y	24
9	abd abscess (15)	8.5	16.6	A	Y (bone)	28
10	N (10)	10.5	2.3	A[c]	Y (lung; LNs)	20
11	N (10)	257.2	2.8	A	N (lung)	18
12	N (14)	8.2	2.3	D	Y (lung)	18
13	N (13)	297.6	4.2	A[c]	N	21
14	N (11)	92.0	1.4	A	N	14
15	SBO (13)	5.6	3.3	A	Y (lung)	18
16	biloma; SBO (10)	3.9	0.3	A[c]	Y (LNs; scar)	14
17	N (11)	3.1	1.9	A	N	16
18	N (24)	8.1	3.0	A	N	11
19	N (11)	0.7	0.6	A	Y (lung)	6
20	N (8)	5.0	-	A	N	1

[a]PE = pulmonary embolism; SBO = small bowel obstruction; Y = yes; N = no.
[b]Died from upper gastrointestinal hemorrhage.
[c]Symptomatic.
[d]LNs = Lymphnode metastases.

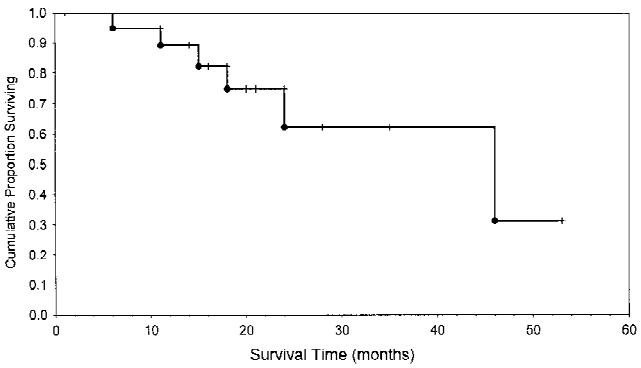

Fig. 1. Survival for patients who had cryotherapy to residual metastases after resection (Kaplan-Meier).

by the dramatic decline in CEA levels after treatment. Although some of the patients developed local recurrence (n = 12) and/or distant metastases (n = 11) within a relatively short time after surgery, it is debatable whether the former were inadequately ablated liver metastases, or whether they were manifestations of previous microscopic disease. Both possibilities, however, support the argument for regional chemotherapy after combined liver resection and cryotherapy.

Adjuvant regional chemotherapy following liver resection has been described by two groups [14,15]. In Wagman's study [14], median time until hepatic recurrence was 30.7 months in patients who had chemotherapy, compared with 8.7 months for patients who had resection alone. It could well be that the regional chemotherapy is at least partly responsible for our results, but the important difference between our study and those cited is that our patients were judged to be irresectable, so they would only have received hepatic artery chemotherapy in isolation as an alternative treatment.

Although this is not a control study, survival would seem to be considerably better than the survival of patients treated by hepatic artery chemotherapy alone, where median survival of <18 months has been seen in almost all series [16,17]. Clearly, survival in our patients is superior to the median survival of only 6–12 months reported for unselected patients with untreated bilobar metastases [6,18,19]. We were also encouraged by the long-term, disease-free interval in a few patients. In fact, the relatively good survival of 88% at 1 year and 60% at 2 years is similar to that after curative liver resection [4,7,17,20]. Longer follow-up should allow us to make more meaningful comparisons.

CONCLUSIONS

Cryotherapy can safely extend the limits of resection in selected patients with multiple bilobar liver metastases with relatively good results.

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